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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/782,184	02/12/2001	Howard Sands	12636-898	6040

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EXAMINER	
GOLLAMUDI, SHARMILA S	

ART UNIT	PAPER NUMBER
1616	

DATE MAILED: 12/04/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/782,184	SANDS ET AL.	
	Examiner	Art Unit	
	Sharmila S. Gollamudi	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 and 6-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 6-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt of Request for Continued Examination and Amendments/Remarks filed 4/10/06 is acknowledged. Claims **1-4 and 6-36** are pending in this application. Claim 5 stands cancelled.

Miscellaneous Remarks

Applicant should note 37 CFR 1.121 when filing amendments to the claims. For instance, "The text of any deleted matter must be shown by strike-through except that double brackets placed before and after the deleted characters may be used to show deletion of five or fewer consecutive characters. A strike-through should be used to delete text with more than five words.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4 and 6-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites, "An injectable pharmaceutical composition comprising: an aqueous suspension of microdroplets suitable for intravenous delivery, wherein the microdroplets are multi-lamellar vesicles comprising a substantially water-insoluble, pharmacologically acceptable lipophilic liquid, a camptothecin dissolved in the water- insoluble, pharmacologically acceptable liquid, and an outer layer comprising a membrane- forming phospholipids. This claim is vague and indefinite since it is unclear if the "substantially water-insoluble, pharmacologically acceptable lipophilic liquid" is the same as the "water- insoluble, pharmacologically acceptable liquid" in which the camptothecin is dissolved in since two different terms are used, i.e. 1)

substantially water-insoluble, pharmacologically acceptable *lipophilic* liquid and 2) water-insoluble, pharmacologically acceptable liquid". If both the insoluble liquids are the same, then the examiner suggests amending the claim to reflect this. If they are not, the examiner points out that in line 5, "the water-insoluble" lacks antecedent basis. Further, the examiner points out that line 6 recites "an outer layer comprising a membrane forming phospholipids" which is vague and indefinite since multilamellar vesicles (MLV), i.e. liposomes, have multiple lipid layers and not just one layer. Lastly, the examiner points out that applicant claims a "microdroplet" which is a MLV, which is confusing since a liposome is not a droplet. Further clarification is requested. The examiner suggests removing the term "microdroplet".

Claim 18 recites, "An injectable pharmaceutical composition comprising: a dispersion in an aqueous carrier solution comprising one or more pharmaceutically acceptable tonicity modifier agents and liquid droplets, the droplets are multi-lamellar vesicles comprising a substantially water-insoluble, pharmaceutically acceptable lipophilic liquid, a camptothecin dissolved in the lipophilic liquid, and an outer layer comprising at least one membrane-forming amphipathic lipid, and wherein upon thermal sterilization the dispersion does not aggregate, flocculate, agglomerate, or coalesce, and the droplets do not grow in size above a volume weighted mean diameter of 10 microns." Further, the examiner points out that line 6 recites "an outer layer comprising a membrane forming phospholipids" which is vague and indefinite since multilamellar vesicles (MLV), i.e. liposomes, have multiple lipid layers and not just one layer. Lastly, the examiner points out that applicant claims a "liquid droplet" which is a MLV, which is confusing since a liposome is not a liquid droplet, rather is a liquid containing vesicle. Further clarification is requested. The examiner suggests removing the term " liquid droplet".

Claim 19 recites, "An injectable pharmaceutical composition comprising: an aqueous carrier solution comprising one or more pharmaceutically acceptable tonicity modifier agents; a dispersion of liquid droplets of a first size distribution, the liquid droplets are multi- lamellar vesicles comprising a substantially water-insoluble, pharmaceutically acceptable lipophilic liquid, solid particles of a camptothecin of a second size distribution, and an outer layer surrounding the droplet comprising at least one membrane- forming amphipathic lipid; wherein the second size distribution is smaller than the first size distribution; and wherein upon thermal sterilization, the dispersion does not aggregate, flocculate, agglomerate, or coalesce, and the droplets do not grow in size above a volume weighted mean diameter of 10 microns." The phrase "liquid droplets are multi-lamellar vesicles" is an unclear term since multi-lamellar vesicles are liquid *containing* vesicles but they are not liquid droplets since they are surrounded by lipid layers. Further clarification is requested. Further, the examiner points out that line 8 recites "an outer layer surrounding the droplet" which is vague and indefinite since multilamellar vesicles (MLV), i.e. liposomes, have multiple lipid layers and not just one layer.

Claim 12 recites the limitation "the pharmaceutically acceptable organic liquid" in line 2. There is insufficient antecedent basis for this limitation in the claim. Further, claim 12 is directed to a pharmaceutically acceptable organic liquid which is selected from of "alkanes, dialkyl ethers, long-chain esters, hydrophobic esters, biocompatible silicones, biocompatible high molecular weight fluorocarbons, oil-soluble vitamins and volatile liquid anesthetics." It is unclear how the pharmaceutically acceptable organic liquid can be another active agent such as a anesthetic. Further clarification is requested.

Lastly, it is noted that the independent claims do not state where the camptothecin is located, i.e. intercalated in the lipid bilayers or in the central cavity; thus both interpretations will be applied.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 8, 12 are rejected under 35 U.S.C. 102(n) as being anticipated by Castor et al (5,776,486).

Castor et al discloses a method and apparatus for making liposomes contains hydrophobic drugs. see abstract. Castor discloses liposomes have multiple bilayers and are known as multilamellar vesicles (MLV) and are excellent carriers for drugs. see column 1, lines 35-45. The examples utilize paclitaxel and camptothecin as the hydrophobic drug. see also column 22, lines 50-55. The ScoCoNC fluid (instant lipophilic liquid) is selected from carbon dioxide, propane, ethane, ethylene, trichlorofluoromethan, dichlorofluoromethane, difluorochloromethane, and trifluoromethane. See column 8, lines 60-66 and examples. Castro disclose a method of forming the liposomes by dissolving the phospholipids, the ScoCoNC fluid, and the drug to form a drug mixture. Then the drug mixture is injected into an aqueous phase to form the liposomes of a maximum diameter of 2.7 microns.. See column 24, lines 10-25 and Table 18. The instant phospholipids are disclosed on column 23, lines 10-15. Castor discloses the aqueous phase is saline.

Claims 1-4, 8, 12-17 are rejected under 35 U.S.C. 102(n) as being anticipated by WO 95/08986.

WO '986 discloses multilamellar vesicles comprising camptothecin. The vesicles are dispersed in an aqueous phase. See abstract and page 2, lines 25-35. The vesicles have a diameter of 0.5-10 microns. See page 3, lines 1-10. The instant phospholipids are disclosed on page 5. Also cholesterol is disclosed on page 5, line19. The instant camptothecin is disclosed on page 9, lines 1-30. WO '986 discloses that the drug concentration may vary from 0.1mg/ml to 10mg/ml. See page 10, lines29-35. Example 1 discloses dissolving DMPC (instant lipophilic ester), DMPG (instant membrane forming phospholipid), and camptothecin to make the MLV. The vesicles are then hydrated in saline. The ratio of DMPC:DMPG:camptothecin is 84.6:9.4:6.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-4, 6-8, 12-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wallach et al (5,628,936) in view of Gregoriadis, G (Liposome Technology, Vols. 3, page 21 and 138, 1984) in further view of Burke (5552156) or vice-versa.

Wallach et al teaches a hydrid paucilamellar lipid vesicle (PLV) containing a phosphor- or glycolipid and a surfactant in the lipid bilyaer. The vesicles have either aqueous or oil-filled central cavity. See abstract. Wallach teaches PLV's, which can be considered a sub-class of the MLV's, possess features of both MLV's and LUV's. PLV's appear to have advantages as transport vehicles for many uses as compared with the other types of lipid vesicles. In particular, because of the large unstructured central cavity, PLV's are easily adaptable for transport of large quantities of aqueous- or oil-based materials. Moreover, the multiple lipid bilayers of the PLV's provides PLV's with additional physical strength and resistance to degradation as compared with the single lipid bilayer of the LUV's. The central cavity of the PLV's can be filled wholly or in part with an apolar oil or wax and then can be used as a vehicle for the transport or storage of hydrophobic materials. The amount of hydrophobic material, which can be transported by the PLV's with an apolar core is much greater than can be transported by MLV's. see column 2, lines 10-45. The instant phospholipids, particularly egg lecithin, are taught on column 5, lines 5-20. Cholesterol is taught on column 5, lines 40-43. The oil-soluble material to be carried is dispersed in the water-immiscible oil and blended in the already formed lipid phase to form a lipophilic phase. Wallach teaches the term "dispersed" means dissolved or suspended. See column 5, lines 45-55. Wallach teaches various oil-based materials, which can form colloids or suspensions in the oil may be used. See column 7, lines 5-25. Wallach teaches a complete listing of the types of pharmaceuticals that could be encapsulated in lipid vesicles is in Gregoriadis, G.,

ed. Liposome Technology (CRC, Boca Raton, Fla.), Vols. 1-3 (1984). Wallach teaches that when the water-immiscible oil is used the oil stabilizes the vesicles, leading to high fracture strength and longer term stability than vesicles made without oil. Wallach teaches the oil-filled vesicles are so stable that paucilamellar oil-filled vesicles can be formed from phospholipids using the methods of the invention without the addition of any non-ionic or zwitterionic surfactant. see column 8, lines 15-30. The water-immiscible liquid include oils, waxes, triglycerides, acyl ethers, petroleum derivatives, peanut oil. See column 5, lines 20-40. Example 2 teaches a diameter of 0.654 microns.

Wallach does not specifically teach the use of camptothecin.

Gregoriadis, teaches the encapsulation of anticancer drugs. See page 21 and 138.

Burke teaches the instant camptothecin drugs encapsulated by lipids to overcome the insolubility and instability problems of camptothecin for intravenous administration. Burke teaches camptothecin is an anti-cancer drug that is water-insoluble that hinders its delivery to cancer cells. See column 1, lines 30-45. Burke states that camptothecin drugs bind the lipid bilayer of liposomes with great affinity and intercalates between the acyl chains of the lipid. Thus, the lactone ring of the camptothecin membrane bound drug is removed from the aqueous environment *inside* and *outside* of the liposome and is protected from hydrolysis, preserving the activity of the drug. Further, Burke teaches reducing the internal pH of the liposome to prevent hydrolysis of certain camptothecin drugs when the drug disassociated from the lipid membrane. See column 3, line 59 to column 4, line 2. Burke teaches the liposomes are stable are an external pH of 7.4 and 5. See column 21, lines 1-3. Thus, the lipid encapsulation creates an internal environment with a low pH to prevent hydrolysis of camptothecin drugs. (Note abstract).

Various drug concentrations are utilized in the examples. Burke teaches the use of unilamellar or multilamellar vesicles wherein the vesicle contains surfactants and phospholipids. Note examples.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teaching of Wallach, Gregoriadis, and Burke and utilize the instant camptothecin in Wallach's PLV. One would have been motivated to do with the expectation of similar results since firstly since Burke teaches camptothecin is a water-insoluble anti-cancer drug and Wallach teaches the incorporation of any water-insoluble drugs and incorporates the teachings of Gregoriadis for the drugs that are suitable for encapsulation. Gregoriadis teaches the encapsulation of anticancer drugs for chemotherapy. Secondly, Burke teaches the advantages of encapsulating water-insoluble camptothecin in phospholipid structures, which allows one to successfully deliver camptothecin by overcoming instability and insolubility problems caused by hydrolysis by the aqueous phase. Thus, a skilled artisan would have been motivated to use Wallach's vesicle to encapsulate camptothecin since the vesicle will prevent hydrolysis of the camptothecin's lactone ring and preserve camptothecin's activity. It should be noted that depending on the type of water-immiscible oil used and the specific camptothecin, camptothecin's dissolution will change from soluble to poorly soluble.

With regard to claims 6-7, a skilled artisan would have been motivated to utilize the instant pH of less than 6 for the injectable carrier since Burke teaches a low pH prevents hydrolysis of camptothecin's lactone ring, thus preserving its activity. Therefore, a skilled artisan would have been motivated to simultaneously also manipulate the pH of the injectable carrier if camptothecin is utilized as the active of choice, to preserve its activity.

With regard to claims 13-17, it is within the skill of an artisan to manipulate the concentration of camptothecin using the guidance provided by Burke since Burke teaches several concentrations of camptothecin. Further, this is deemed to be a manipulatable parameter, which is known to those skilled in the art.

Alternatively, Burke does not teach a pharmaceutically acceptable lipophilic liquid in combination with the phospholipids. However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine Burke et al and Wallach et al and a specifically add a water-immiscible oil to displace a portion of the aqueous phase. One would have been motivated to do so since Wallach teaches this stabilizes the vesicle, leading to high fracture strength and longer term stability than vesicles made without oil. A skilled artisan would have reasonably expected success since both Burke and Wallach teaches the use of MLV (note a PLV is a subclass of MLV) as carriers for hydrophobic drugs.

Claims 9-11 and 18-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wallach et al (5,628,936) in view of Gregoriadis, G (Liposome Technology, Vols. 3, page 21 and 138, 1984) in view of Burke (or vice-versa as applied above) in further view of WO 99/61001.

The teachings of Wallach, Gregoriadis, and Burke have been set forth above.

The references do not teach the inclusion of tonicity modifiers (mannitol or trehalose) as claimed in independent claims 18-19 or thermally sterilizing the composition as claimed in dependent claims 10-11.

WO 99/61001 teaches suspensions of submicron and micron sized particles of water insoluble biologically active substances that are stabilized by thermoprotecting agents, and that

can be terminally steam sterilized without any significant increase of mean particle size. These compositions display markedly reduced heat-induced coagulation, flocculation, or particle size growth during the terminal steam sterilization process. WO teaches it is necessary to sterilize parenteral composition. However, during this process surfactants on the surface of the particle are released. The particles that are devoid of the surfactant become unstabilized and grow in size. See pages 1-2. WO's invention is directed to stabilizing particles that utilize only phospholipids as surfactants. Specifically egg lecithin (Lipoid) is disclosed. See Table 1. Examples of suitable thermoprotecting agents include one or a combination of pharmaceutically acceptable water-soluble polyhydroxy compounds that also act as tonicity modifiers such as dextrose, sucrose, mannitol, sorbitol, and lactose. The reference teaches including these agents for protection during sterilization (note the abstract, examples and claims). The reference also teaches the use of Lipoid E80 (Table 1). WO teaches that the formulation may contain suitable amount of buffering salts and pH adjusting agents since it is known to those skilled in the art of phospholipids that a pH lower than 5 and higher than 9, the phospholipids molecules undergo extensive hydrolysis. Therefore, the pH of the suspension is usually adjusted to within this range prior to homogenization. See page 15.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the above references and include tonicity modifiers such as trehalose or mannitol in the composition. One would have been motivated to do so since WO teaches that the instant sugars are thermoprotectants and protect the phospholipid particle suspensions during sterilization, which is a necessary step for parenteral compositions.

Claims 6-7, 9-11, 18, 20-27, 30-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 95/08986 in view of WO 99/61001.

The teachings of WO '986 has been set forth.

The reference do not teach the inclusion of tonicity modifiers (mannitol or trehalose) as claimed in independent claims 18-19 or thermally sterilizing the composition as claimed in dependent claims 10-11. Further, WO '986 does not specify the pH of the aqueous phase.

WO 99/61001 teaches suspensions of submicron and micron sized particles of water insoluble biologically active substances that are stabilized by thermoprotecting agents, and that can be terminally steam sterilized without any significant increase of mean particle size. These compositions display markedly reduced heat-induced coagulation, flocculation, or particle size growth during the terminal steam sterilization process. WO teaches it is necessary to sterilize parenteral composition. However, during this process surfactants on the surface of the particle are released. The particles that are devoid of the surfactant become unstabilized and grow in size. See pages 1-2. WO's invention is directed to stabilizing particles that utilize only phospholipids as surfactants. Specifically egg lecithin (Lipoid) is disclosed. See Table 1. Examples of suitable thermoprotecting agents include one or a combination of pharmaceutically acceptable water-soluble polyhydroxy compounds that also act as tonicity modifiers such as dextrose, sucrose, mannitol, sorbitol, and lactose. The reference teaches including these agents for protection during sterilization (note the abstract, examples and claims). The reference also teaches the use of Lipoid E80 (Table 1). WO teaches that the formulation may contain suitable amount of buffering salts and pH adjusting agents since it is known to those skilled in the art of phospholipids that a pH lower than 5 and higher than 9, the phospholipids molecules undergo

extensive hydrolysis. Therefore, the pH of the suspension is usually adjusted to within this range prior to homogenization. See page 15.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teaching of WO '986 and WO '001 and include tonicity modifiers such as trehalose or mannitol in the composition. One would have been motivated to do so since WO teaches that the instant sugars are thermoprotectants and protect the phospholipid particle suspensions during sterilization, which is a necessary step for parenteral compositions.

With regard to claims 6-7, a skilled artisan would have been motivated to utilize the instant pH for the injectable carrier since WO '001 teaches it is known in the art to utilize a pH of 5 to 9 to prevent hydrolysis of camptothecin's lactone ring, thus preserving its activity of the drug. Therefore, a skilled artisan would have been motivated to simultaneously also manipulate the pH of the injectable carrier if camptothecin is utilized as the active of choice, to preserve its activity.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharmila S. Gollamudi whose telephone number is 571-272-0614. The examiner can normally be reached on M-F (8:00-5:30), alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Sharmila S. Gollamudi
Examiner
Art Unit 1616